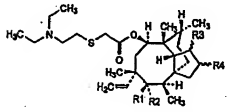
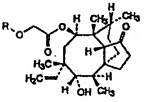
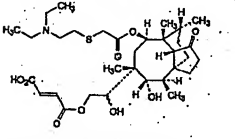


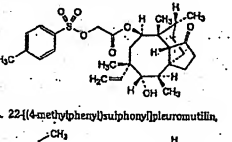
F. R1 + R2 = O, R3 = OH, R4 = H: (3a*S*,4*R*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-1-hydroxy-4,6,9,10-tetramethyl-5-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulphanyl]acetate,



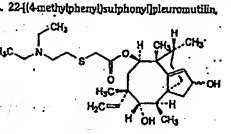
I. R1 = H, R2 = R3 = OH, R4 = O-CO-CH=CH-CO_2H: 2,3-dihydroxytiamulin 2-fumarate,



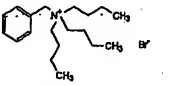
H. 19,20-dihydroxytiamulin 20-fumarate,



L. 22-[(4-methylphenyl)sulphonyl]pleuromutilin,



Q. Tiamulin-3-en-2-ol,



R. (phenylmethyl)(tributyl)ammonium bromide.

Reference: PA/PH/Exp. 30b/T (01) 9 ANF

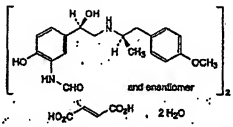
NOTE ON THE MONOGRAPH

Tiamulin base is applied parenterally either as a subcutaneous or an intramuscular, oily injection.

XXXX:1724

FORMOTEROL FUMARATE DIHYDRATE

Formoteroli fumaras dihydras



$C_{42}H_{56}N_4O_{12},2H_2O$ M_r 840.9

DEFINITION

N[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (*E*)-2-butenedioate dihydrate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white or slightly yellow powder.

Solubility: slightly soluble in water, freely soluble in dimethyl sulphoxide, soluble in methanol, slightly soluble in 2-propanol, practically insoluble in acetonitrile.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: Ph. Eur. reference spectrum of formoterol fumarate dihydrate.

TESTS

pH (*2.2.3*): 5.5 to 6.5.

Dissolve 20 mg in *carbon dioxide-free water R* while heating to about 40 °C and dilute to 20 ml with the same solvent. Allow to cool.

Optical rotation (*2.2.7*): −0.10° to + 0.10°.

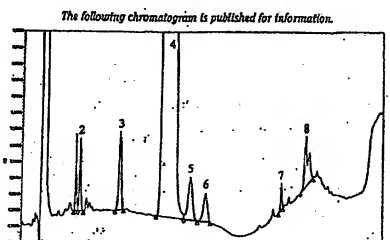
Dissolve 0.25 g examined in *methanol R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Solution A. Dissolve 6.10 g of *sodium dihydrogen phosphate monohydrate R* and 1.03 g of *disodium hydrogen phosphate dihydrate R* in *water R* and dilute to 1000 ml with the same solvent. The pH is 6.0 ± 0.1.

Solvent mixture. Acetonitrile R, solution A (16:84 *V/V*).

The following chromatogram is published for information.



1. impurity C
2. impurity A
3. impurity B
4. formoterol
5. impurity C
6. impurity D
7. impurity E
8. impurity F

Figure 1724.-1. – *Chromatogram obtained with reference solution (a) in the test for related substances*

Test solution. Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 ml with the solvent mixture. *This solution must be injected within 4 h from preparation, or stored protected from light at 4 °C for not more than 24 h.*

Reference solution (a). Dissolve 5 mg of *formoterol fumarate for system suitability CRS* in the solvent mixture and dilute to 25.0 ml with the solvent mixture.

Reference solution (b). Dilute 1.0 ml of the test solution to 25.0 ml with the solvent mixture. Dilute 1.0 ml to 20.0 ml with the solvent mixture.

Column:

- *size:* l = 0.15 m, Ø = 4.6 mm;
- *stationary phase:* spherical *octylsilyl silica gel for chromatography R3* (5 µm)[13] with a pore size of 8 nm.

Mobile phase:

- *mobile phase A: acetonitrile R1*,
- *mobile phase B:* dissolve 3.73 g of *sodium dihydrogen phosphate monohydrate R* and 0.35 g of *phosphoric acid R* in *water R* and dilute to 1000 ml with the same solvent; the pH is 3.1 ± 0.1.

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 10	16	84
10 - 37	16 → 70	84 → 30
37 - 40	70 → 16	30 → 84
40 - 55	16	84

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µl.

Retention time: formoterol = about 12 min.

(13) Kromasil 5SC$_8$ is suitable.

System suitability: reference solution (a):

- *resolution:* minimum 1.5 between the peaks due to impurity G and to impurity A.

Limits:

- *correction factor:* for the calculation of content, multiply the peak area of impurity A by 1.75,
- *impurity A:* not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *impurity B, C, D or F:* for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent); use the chromatogram obtained with reference solution (a) to identify the corresponding peaks,
- *any other impurity:* not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *total:* not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
- *disregard limit:* 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity I. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 mg of the substance to be examined in *water R* and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dissolve 5.0 mg of *formoterol impurity I CRS* in *water R* and dilute to 50.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of the test solution to 20.0 ml with *water R*. Dilute 1.0 ml of this solution to 25.0 ml with *water R*.

The following chromatogram is published for information.

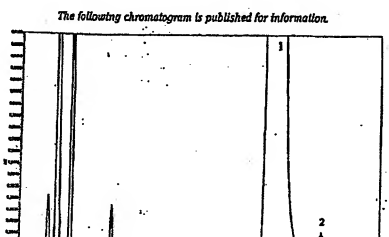


Figure 1724.-2. – *Chromatogram obtained with reference solution (a) in the test for impurity I*

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,

– *stationary phase*: *octadecylsilyl vinyl polymer for chromatography R*(18).

Mobile phase: mix 12 volumes of *acetonitrile R1* with 88 volumes of a 5.3 g/l solution of *tripotassium phosphate trihydrate R* previously adjusted to pH 12.0 ± 0.1 with a 280 g/l solution of *potassium hydroxide R* or *phosphoric acid R*.

Flow rate: 0.5 ml/min.

Detection: spectrophotometer at 225 nm.

Injection: 20 µl.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 3.5, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol.

Limits:

– *impurity I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.32*): 4.0 per cent to 5.0 per cent, determined on 50 mg.

ASSAY

Dissolve 0.350 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 40.24 mg of $C_{42}H_{52}N_4O_{12}$.

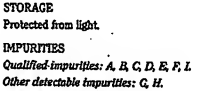
STORAGE

Protected from light.

IMPURITIES

Qualified impurities: *A, B, C, D, E, F, I.*

Other detectable impurities: *G, H.*



A. R1 = R2 = R4 = H, R3 = CH_3: 1-(3-amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol,

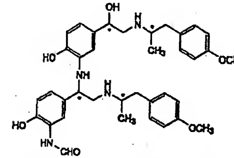
B. R1 = CHO, R2 = R3 = R4 = H: *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide,

C. R1 = CO-CH_3, R2 = R4 = H, R3 = CH_3: *N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]acetamide,

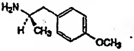
D. R1 = CHO, R2 = R3 = CH_3, R4 = H: *N*-[2-hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,

E. R1 = CHO, R2 = H, R3 = R4 = CH_3: *N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,

(18) Ashbigh ODP-50 or Astec Polymer C_{18} are suitable.

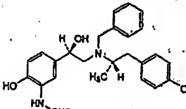


F. *N*-[2-hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide,



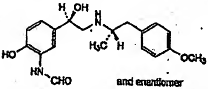
and enantiomer

G. (2*RS*)-1-(4-methoxyphenyl)propan-2-amine,



and enantiomer

H. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (monobenzyl analogue),



and enantiomer

I. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*SR*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (diastereoisomer).

Reagents

Silica gel for chromatography, octylsilyl R3. *XXXXXXX*.
A very finely divided ultra pure silica gel, chemically modified at the surface by the bonding of octylsilyl groups and sterically protected with branched hydrocarbons at the silanes. The particle size is indicated after the name of the reagent in the tests where it is used.

Tripotassium phosphate trihydrate. $K_3PO_4,3H_2O$. *XXXXXXX*. [22763-03-7].
White or almost white crystalline powder, freely soluble in water.

Reference: PA/PH/Exp. 10C/T (97) 19 ANP 1R

NOTE ON THE MONOGRAPH

A new draft monograph on Metolazone, previously published in Pharmeuropa 11.3, is proposed.

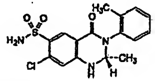
Metolazone exhibits polymorphism. The α-form has a low solubility and a slower dissolution rate than the γ-form and should be limited. It is proposed to introduce a limit test for α-metolazone by IR.

A new HPLC test for related substances is presented together with revised specifications according to batch data.

XXXX:1757

METOLAZONE

Metolazonum



and enantiomer.

$C_{16}H_{16}ClN_3O_3S$ M_r 365.8

DEFINITION

(2*RS*)-7-Chloro-2-methyl-3-(2-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulphonamide.

Content: 97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellowish, crystalline powder.

Solubility: very slightly soluble in water, soluble in methanol, slightly soluble in ethyl acetate, very slightly soluble in methylene chloride.

mp: about 256 °C.

It shows polymorphism.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: mulls in *liquid paraffin R*.

Comparison: *metolazone CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

α-Metolazone: Infrared absorption spectrophotometry (*2.2.24*).

Preparation: mulls in *liquid paraffin R*.

Draw the baseline between the transmission maxima at 813 cm^{-1} and at 649 cm^{-1}. Calculate *R* using the expression:

$$1 - \frac{T_1 - T_2}{T_3 - T_2}$$

T_1 = percentage transmittance at the transmission minimum at 801 cm^{-1},

T_2 = percentage transmittance at the transmission minimum at 781 cm^{-1},

T_3 = percentage transmittance of the baseline of the transmission minimum at 801 cm^{-1}.

R is not more than 0.15.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 320.0 mg of the substance to be examined in *dimethylformamide R* and dilute to 100.0 ml with the same solvent.